REMARKS

In connection with the Office Action dated April 19, 2005, the Examiner has:

(1) rejected claims 44, 51-52, and 59 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to reasonably convey to the skilled artisan that the Applicants had possession of the claimed invention at the time of filing;

(2) rejected claims 44-45, 47, 49-53, 55, and 57-59 under 35 U.S.C. § 102(b) as being anticipated by Wright et al. (Crit. Rev. Immunol., 12(3,4):125-168, 1992);

(3) rejected claims 44-45, 47, 49-53, 55, and 57-59 under 35 U.S.C. § 102(b) as being anticipated by Stevenson et al. (Ann. N.Y. Acad. Sci., 772:212-226, 1995); and

(4) rejected claims 44-45, 47, 49-53, 55, and 57-59 under 35 U.S.C. § 102(b) as being anticipated by Chen et al. (Proc. Natl. Acad. Sci. USA, 91:5932-59-36, 1994) or Chen et al. (Human Gene Therapy 7:1515-1525, 1996).

Claims 44-45, 47, 49-53, 55, and 57-59 are pending in the application. In the present response, claims 44 and 52 have been amended, and claims 50-51 and 58-59 have been cancelled. No new matter has been added. Upon entry of the amendment, claims **44-45, 47, 49, 52-53, 55, and 57** remain pending in the present application. Applicant requests reconsideration in view of the following remarks and foregoing amendment.

35 U.S.C. § 112

With respect to item (1), the Examiner has rejected claims 44, 51-52, and 59 under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification in such a way as to reasonably convey to the skilled artisan that the Applicants had possession of the claimed invention at the time of filing.

Claims 44 and 52 have been amended and claims 51 and 59 have been cancelled. In view of the amendment, the issues raised by the Examiner in connection with these claims are now moot.

35 U.S.C. § 102

With respect to items (2), (3) and (4), the Examiner has asserted that claims 44-45, 47, 49-53, 55, and 57-59 are anticipated by Wright et al., Stevenson et al., Chen et al. (1994) and Chen et al. (1996). Applicants respectfully disagree.

The claims, as set forth, require transplantation of a modified cell (non-B cell) such that antibody can be secreted and enter the blood circulation of the mammal. The cited references, on the other hand, disclose and teach only the production of antibodies in cell culture. The references fail to teach transplantation of the cell, such that the antibody can be produced in vivo. For example, Wright et al. discuss scale-up methods for production of antibodies, and further suggest the possibility of using serum-free media culture to facilitate antibody purification.

Moreover, there was no suggestion or teaching in any of the references whether modified non-B cells may be used for transplantation and production of an antibody in vivo. To this end, prior to the time of filing, there would have been no motivation to extend the teachings of the references, and to use the modified cells for transplantation and for in vivo production of antibodies. This is because one of ordinary skill in the art would have expected, without evidence to the contrary, that genetically modified non-B cells would be eliminated in vivo by various immunological mechanisms, that antibodies produced within cells in vivo would not be secreted by the non-B cells, that secreted antibodies would be maintained within the tissular interstitial areas or within the extracellular matrix, that antibodies produced by non-B cells would be produced abnormally in a structural and functional sense, and that an anti-idiotypic response could be elicited.

In order to highlight certain aspects of the present invention and the state of the art at the time of the filing of the application, the following brief, non-limiting description is provided. The claimed invention, as set forth in the present application, relates to the novel concept of producing antibodies in mammals by cells that are not specialized for naturally producing antibodies (i.e., non-plasmocytes or non-B cells). There are a few important points to keep in mind. The first is the production of antibodies within living mammals via gene/cell therapy approaches using non-B cells. The second is the absence of detectable adverse reactions from the

host against both the ectopic antibody (as judged from the absence of anti-idiotypic responses), and the modified cells after grafting (as judged from the stability of production over time).

At the time of filing, it was known that different types of proteins could be produced by cells not naturally specialized in that particular protein function. However, there was no evidence that what was observed for a non-antibody protein could be predictably extrapolated to antibodies being produced in non-B type cells. Accordingly, there was a need to demonstrate that antibodies displaying characteristics comparable to those of antibodies produced by plasmocytes, i.e., B-cells, could be produced by genetically modified non-B cells in vivo, and that these antibodies would be capable of migrating to the blood stream of a mammal.

Furthermore, at the time of filing of the claimed invention, a skilled artisan would not have expected that one would have been able to produce antibodies that were able to reach the blood circulation in living mammals through use of cells that are not specialized in naturally producing antibodies (non-B cells). This is because:

Plasmocytes are cells of the B cell lineage that are specialized in the synthesis and secretion of antibodies. Plasmocytes are in direct contact with the blood. Therefore, there is no special hurdle to overcome to have the antibody released in the blood stream. The plasmocytes, however, cannot be used for gene therapy for at least two reasons: (i) they already produce an antibody and (ii) they are short-lived (a few days to a few weeks). In connection with the first reason, genetic modification of plasmocytes for production of another antibody would be met with a serious "conflict of interest" between the two antibodies produced by the same cell. Moreover, antibodies with double specificity of recognition (as we would have to deal with populations of primary plasmocytes directed against a multitude of different antigens), would likely be produced. In connection with the second reason, the treatment must be readministered every few weeks, which cannot be considered in the context of gene therapy. As such, it must be demonstrated that non-B cells that could be used in a gene therapy protocol can be adapted for the production of high quality antibodies that could reach the blood stream.

It should be noted that at the time of filing of the present invention, there was no information readily available in the art which indicated that the complex process of production and secretion of antibodies (Abs), which appeared to be related to a specialized pathway of B cells, could be considered in the context of non-B cells. Indeed, after mRNA translation, the different chains of an antibody must : (i) associate with the endoplasmic reticulum, (ii) form tetramers (for natural antibodies: 2 light + 2 heavy chains), (iii) be subjected to various post-translational modifications (serial glycosylations at various sites), (iv) interact with molecular chaperones permitting their correct folding, (v) migrate to the cell surface and (vi), at last, be released in the extracellular medium in a form preserving their ability to recognize efficiently their antigen.

It was important to consider that the Abs could be trapped either in the compact structure of tissues and organs where they were produced, in interstitial spaces of these organs, or in the extracellular matrix surrounding the non-B cells producing them. It was also considered that the Abs could be degraded (trapped or not in interstitial tissue spaces) by extracellular proteases contained in tissues not specialized in their production, as is the case of certain other proteins.

It could not be stated, however, that Abs produced by non-specialized cells would not be recognized as foreign (non-self) elements and, therefore, would not induce an anti-idiotypic response against them. For example, it could be imagined that Abs could be subjected to abnormal post-translational modifications during their synthesis. As already mentioned, antibodies harbor numerous post-translational modifications, notably glycosylations that account for 2 to 14% of their molecular weight. Improper post-translational modifications could have favored the generation of anti-idiotypic responses possibly neutralizing the ectopically produced Ab. In the case of therapeutic Abs, this would lead to reduction or suppression of treatment efficiency. Moreover, it could be feared that the presence of Abs at the surface of non-B cells (at the time the antibody is secreted) may itself favor the recognition of the Ab as a foreign antigen and, thereby, giving rise to the emergence of an anti-idotypic response against it. Immune responses against ectopic proteins have, indeed, already been observed in various gene therapy protocols.

Therefore, the problem to solve was to demonstrate that cells which could be used in gene therapy protocols, and not naturally producing antibodies, are capable of producing Abs which are functional, capable of reaching the blood stream and which do not induce an adverse reaction (anti-idiotypic response) because they are recognized as non-self.

Accordingly, to establish proof of concept of the claimed invention, the myogenic C2C12 cell line grafted to syngeneic mice has been chosen as a model system. In particular, these cells were a model cell line that was largely used in the field of gene therapy for proofs of concept owing to their ability to form muscular fibers after grafting. The fact that C2C12 cells could form tumors was not a real concern because, on one hand, not all animals develop tumors, and, on the other hand, tumor development takes several months. Moreover, it has been demonstrated, by following the same guidelines set forth in the specification, use of non-tumorigenic primary myoblasts for producing antibodies. This is reported in the publication Noël et al. (1997). In this publication, the experiments conducted with C2C12 cells were included.

After the experiments with the myogenic cells, mAb production were obtained in mice using primary skin fibroblasts (Noel, 2000), primary keratinocytes in the form of reconstituted skin (Noel, 2001), and true hepatocytes (Noel, 2002). These cellular types are relevant for human gene therapy as they are genetically modifiable (often via different approaches) and show a long life span. Therefore, no frequent readministrations of the treatment is necessary. In addition, different gene transfer approaches have been used: (i) ex vivo cell modification by retroviral vectors (Noel, 1997, 2000, 2001), (ii) in vivo modification by recombinant adenoviruses (muscular and liver production of mAbs; Noel, 2002) and (iii) in vivo electroporation of the muscle (Perez et al., 2004). In none of these approaches was there a problem with tumor formation.

With regards to the teachings in the specification of the present invention, the aim was to develop a generic approach to produce mAbs of high quality and have them released in the blood stream of mammals. Such an approach involves gene transfer and is independent of the antigen recognized. The selection criteria of the model mAb for the proof of concept included the following: (i) a mAb for which an ELISA assay was available for monitoring its concentration in

the blood stream + other ELISAs for the monitoring of a possible anti-idiotypic response against it, (ii) a mouse mAb to avoid any immune response against the immunoglobulin backbone (as would have occurred if a human one were to be used) as the experiments were conducted in the mouse and (iii) a mAb for which a BiaCore assay was possible, as it was necessary to demonstrate that the kinetic and thermodynamic properties of a mAb produced in vivo by non-B cells were comparable to that of an antibody produced by a cell of the B lineage (plasmocyte). This is why the Tg10 mAb, a mouse IgG2a/k antibody, and which recognizes the human thyroglobulin was used.

By following the guidelines set forth in the specification, it was demonstrated that antibodies can be produced in genetically modified cells, wherein the cells are not specialized in naturally producing antibodies, and furthermore, that the cells can secrete the antibodies in such manner that they reach/enter the blood circulation. A variety of different types of non-B cells were utilized in this demonstration for both ex vivo and in vivo protocols.

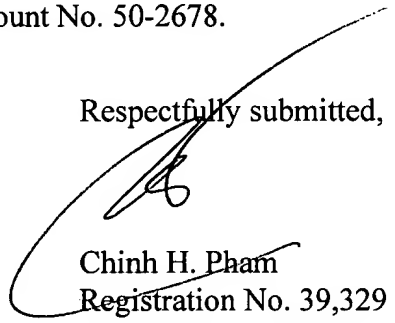
Conclusion

In view of the foregoing amendments and remarks, Applicants submit that the pending claims clearly and distinctly set forth the subject matter of the present invention, and are not rendered anticipated by Wright et al., Stevenson et al., Chen et al. (1994) and/or Chen et al. (1996).

Accordingly, Applicants submit that the claims are now in condition for allowance. Withdrawal of the pending rejections, and early and favorable reconsideration are respectfully solicited. In the event that a telephone conversation would further prosecute and/or expedite allowance, the Examiner is invited to contact the undersigned at (617) 310-6000.

Applicants hereby request a one month extension of time under 37 C.F.R. § 1.136 and authorize the Examiner to charge $60.00 to Deposit Account No. 50-2678 to cover the extension fee. Applicants do not believe that any additional fee is required in connection with this Response. However, should any extension or fee be required, Applicant hereby petitions for same and requests that such and any other fee required for timely consideration of this application be charged to Deposit Account No. 50-2678.

Respectfully submitted,



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